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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,920	09/24/1999	SERGE CARILLO	ST94037A-US	1045

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EXAMINER
BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/405,920	Applicant(s) CARILLO ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2001 and 11 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and arguments received on 10/11/01 have been entered. In regards to applicant's request to withdraw the Notice of Abandonment mailed on 10/3/01 in view of applicant's evidence that a response to the Office action mailed on 3/28/01 was received by the Patent Office on 9/28/01, the Notice of Abandonment is rescinded and prosecution on the merits is resumed. Claims 18-29 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 21-22, and 28-29 under 35 U.S.C. 112, first paragraph, for lack of written description of "parts" of calpastatin that inhibit calpain such that p53 degradation is inhibited is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that since the applicants provide the sequence of calpastatin, SEQ ID NO:1, any fragment of calpastatin can be derived. The applicant further argues that a fragment of

calpastatin with the ability to specifically inhibit degradation of wild-type p53 by calpain is disclosed as SEQ ID NO:3 or 4 on page 7 of the specification. Page 7, however, does not teach or demonstrate that the fragment of calpastatin disclosed as SEQ ID NO:3 or 4 has any p53 degradation inhibitory activity. The specification only states that derivatives of the compounds encoded by SEQ ID NO:2 or 4 which have the ability to inhibit calpain dependent degradation of p53 may be preferentially used in the instant invention. Neither page 7 of the specification, nor the specification as a whole demonstrates that any portion of calpastatin, including the proposed portion corresponding to SEQ NO:3 or 4, has any ability to inhibit calpain dependent degradation of p53. As discussed in the previous office action, fragments of calpain inhibitors and fragments of calpastatin capable of inhibiting calpain and further regulating cellular levels of p53 have not been disclosed by the specification and were not reported in the literature at the time of filing. Further, neither the specification nor the prior art teaches which regions of calpastatin or any other calpain inhibitor are responsible for calpain inhibition and p53 regulation or provide guidance as to the physical characteristics of such fragments including amino acid or nucleic acid sequence. The applicant is reminded that the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of applicants filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff

v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998). Applicant's assertion that fragments can be made does not overcome the lack of description for functional fragments which can inhibit calpain and further regulate p53 protein in a cell. Therefore, only full length human calpastatin meets the written description provision of 35 U.S.C. 112, first paragraph.

The rejection of claims 18-29 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant reiterates their arguments that clinical trial data is not required to satisfy enablement of the instant invention and that the papers in support of the unpredictability of gene therapy methods rely on the FDA standard and not the PTO standard. This is an incorrect interpretation of the teachings of cited references and of the office's position in this case. As stated in the previous office action, the office has neither requested nor required clinical trials and FDA standards of effectiveness have not been applied to the instant case. The office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the Marzocchi decision sanctions

both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). The cited references, Verma et al., Orkin et al., Dachs et al.,and Marshall et al., teach the unpredictability of achieving therapeutic levels of expression of a transgene in vivo by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector. The references base their analysis of the state of the art of gene therapy not simply on clinical trial data, but also on data from in vitro studies and in vivo studies in art accepted animal models. Thus, the papers do not rely on any particular standard, FDA or otherwise, but simply review the problems associated with gene therapy using recombinant vectors at the time of filing. Furthermore, in regards to applicant's citation of In re Brana, it is also pointed out that In re Brana states that if a compound exhibits some desirable pharmaceutical property in a standard experimental animal it has made a significant and useful contribution to the art. Such is not the case in the instant application. The specification fails to provide any *in vitro* or *in vivo* data using the disclosed vectors. It is well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence in the specification which supports that vectors encoding a protein capable of inhibiting both wild type

or mutant p53 degradation in any type of cell *in vivo* can be readily obtained without undue experimentation. Please note that case law teaches that while working examples are not required, ".. the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them". *Ex parte Sudilovsky* (BdPatApp&Int) 21 USPQ2d 1702, citing *In re Novak*, 306 F.2d 924, 134 USPA 335 (CCPA 1962) 4 and *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

The applicant further argues that only routine experimentation would be required to determine which inhibitors of calpain would further have the ability to inhibit p53 degradation, which vector/promoter combinations would be useful for expressing the calpain inhibitors in cell both in vitro and in vivo, the level of calpain inhibitor gene expression that correlates with inhibition of degradation of both mutant and non-mutant forms of p53, and the level of p53 degradation inhibition which correlates with any effect on tumor growth in vitro or in vivo. Case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves. In re Gardner 166 USPQ 138 (CCPA) 1970. The specifications working examples utilize purified calpastatin protein in cell free in vitro assays. While the specification provides a working example which discusses the construction of a recombinant adenoviral vector encoding calpastatin, the specification does not

provide any data regarding the activity of this vector, its capacity to infect and express calpastatin in any and all cells, and the level of calpastatin produced in the various cell types. Further, the specification does not provide any guidance concerning the level of calpastatin expression that correlates with an effect on p53 degradation in intact cells. The specification also teaches that the disclosed vectors can be administered in vivo for the purpose of increasing levels of p53 in tumor cells, particularly tumor cells with one mutated and one wild type copy of p53, such that apoptosis is induced. The specification fails to provide sufficient guidance for routes of vector administration such that tumor cells are transfected/transformed in vivo, or provide guidance as to the level of calpastatin expression and the level of inhibition of calpain dependant p53 degradation that correlates with increased apoptosis in the presence of mutated p53.

Thus, in view of the high level of unpredictability in achieving therapeutic levels of gene expression in particular target cells, and the lack of guidance in the specification for the parameters affecting gene delivery, such as sites and frequency of administration, the dosage of transduced cells or recombinant DNA, appropriate promoter/enhancer combinations and the level of calpain inhibitor expression required to achieve an effect on p53 cellular levels, the lack or working examples, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to use the invention as claimed.

The rejection of claims 18-25 under 35 U.S.C. 112 second paragraph, for indefiniteness is withdrawn in view of applicant's amendment to the claims.

The rejection of claims 26, 28, and 29 under 35 U.S.C. 102(b) over Asada et al. is withdrawn in view of applicant's amendment to the claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should

be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the group fax number is (703) 308-8724.

Dr. A.M.S. Beckerleg

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER